Perfusion Cardiac Magnetic Resonance as a first line technique for the assessment of suspected ischemic heart disease

By Dr E Nagel, Dr. M Kolentinis, Dr. E Vidalakis & Dr. V Puntmann

Perfusion imaging with cardiovascular magnetic resonance (perfusion-CMR) is a diagnostic test for myocardial ischemia, which can be performed rapidly (within approximately 30 minutes) and without using ionizing radiation. It provides highly accurate, strong prognostic data and elucidates the cause of symptoms, such as chest pain, so reducing the need for unnecessary coronary angiographies. Perfusion-CMR is attractive for a wide range of patients as a first line work-up method for their symptoms. A recent international clinical effectiveness trial in 918 patients, who presented with chest pain and intermediate to high pretest probability for coronary artery disease (CAD) has demonstrated the non-inferiority of perfusion-CMR in comparison to an invasive strategy based on fractional flow reserve to guide patient management. Perfusion-CMR demonstrated a high positive predictive value for the presence of significant coronary artery disease and a high negative predictive value for the occurrence of events. A positive test result should be followed by coronary angiography, most likely with revascularization. A negative test result aids in the diagnosis of the underlying, non-coronary, origins of the pathology, such as micro-vascular disease or inflammation, which could explain the patients' symptoms and guide therapy.

The Authors

Dr. Eike Nagel, Dr. Michalis Kolentinis, Dr. Eleftherios Vidalakis & Dr. Valentina Puntmann

Institute for Experimental and Translational Cardiovascular Imaging;

DZHK (German Centre for Cardiovascular Research);

Centre for Cardiovascular Imaging,

Partner Site: Rhine/Main University Hospital Frankfurt, Frankfurt am Main, Germany

Corresponding Author:

Dr. Eike Nagel
Email: *eike.nagel@cardiac-imaging.org*

BACKGROUND EVIDENCE

Numerous studies involving a total of more than 4000 patients have evaluated the diagnostic accuracy and predictive value of perfusion-CMR, with coronary angiography being used as the reference standard, with or without additional fractional flow reserve (FFR). Meta-analyses show sensitivities of 89% (88-91%), specificities of 76% (73-78%) and accuracies of 86% versus coronary angiography [1], with slightly improved values being obtained with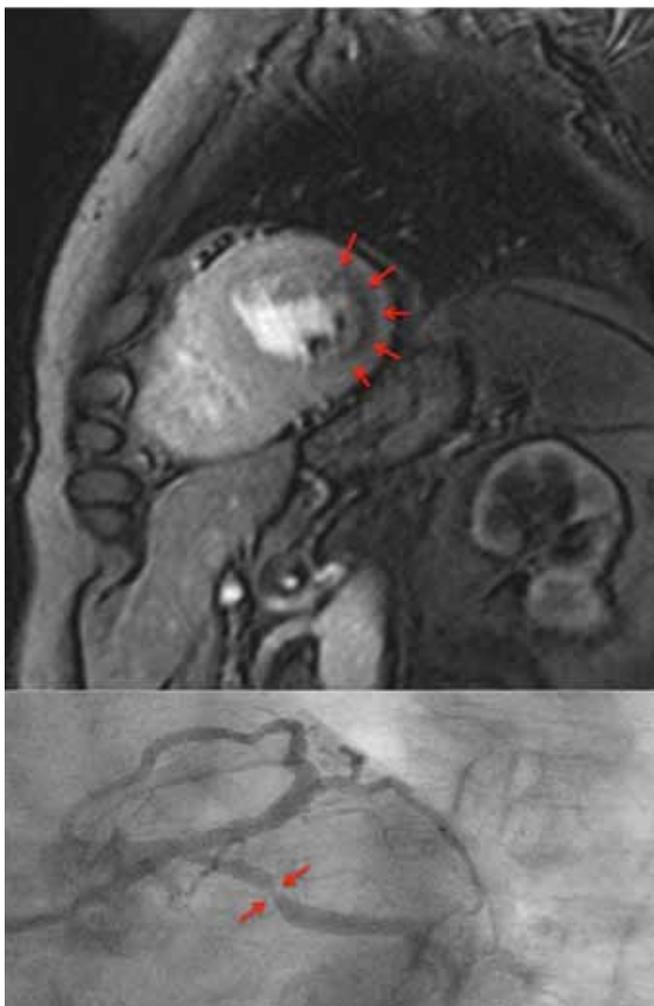 higher field strengths (3 Tesla versus 1.5 Tesla) or with stricter angiographic criteria (70% stenosis versus 50% stenosis) [2]. Similarly, the data are slightly improved when FFR is used as the reference standard (89%/87%/88%) [3]. The diagnostic accuracy was not affected by sex (similar for men and women) or the number of epicardial vessels involved. Perfusion CMR has demonstrated superior diagnostic accuracy compared to SPECT in two large studies, namely the multicenter MR-IMPACT II [4] and the single center CE-MARC [5], as well as in multiple smaller studies summarized in meta-analyses [2,3].

Similarly, Lipinski *et al.* summarized the finding of 19 studies of prognosis and demonstrated the strong prognostic power of perfusion-CMR [6]. In this meta-analysis, 11636 patients who had an average follow-up time of 32 months, showed very low event rates for cardiovascular death 0.3±0.3% and for myocardial infarction 0.4±0.3% when they had a negative CMR result (0.8±0.7% for the combined end-point of cardiovascular death or myocardial infarction). On the contrary, with a positive perfusion CMR event rates were 2.8±1.6%, 2.6±2% and 4.9±3.1% respectively (p<0.0001 for all), resulting in hazard ratios of 7.7, 6.96 and 6.5. Similar to SPECT, ischemia of ≥10% of myocardium in perfusion-CMR denotes the cut-off percentage where revascularization may improve the outcome [7]. The presence of a previous myocardial infarction or diffuse fibrosis/edema adds additional prognostic value [8].

Figure 1. Top panel: Perfusion-CMR during adenosine stress of a patient in the MR-INFORM trial. The CMR study (upper panel) is clearly positive (red arrows demonstrate hypoperfused territory). The patient proceeded to invasive angiography (lower panel) demonstrating a significant stenosis of the circumflex artery (red arrows). Image copyright: Eike Nagel, on behalf of the MR-INFORM investigators.

than in the FFR-informed arm (35.7% in the MR guided group vs. 45.0% in the invasively guided group, p=0.005). There was no significant difference between perfusion-CMR or FFR-guided therapy regarding the occurrence of symptoms such as angina pectoris (50.8% vs. 56.2%, p=0.21) or major adverse cardiac events (death, myocardial infarction, target vessel revascularization) (3.56% vs. 3.72%, HR:-2.68 – 2.36 p=ns) [Figure 2]. These data show that perfusion-CMR is a safe and effective alternative to invasive, FFR-supported coronary angiography in the guidance and optimal management of patients with stable chest pain.

Analysis of the cost-effectiveness of the MR-INFORM trial is still outstanding, but calculations based on the CE-MARC [10] and the Euro-CMR data [11] and in comparison to CTA [12] clearly indicate cost savings for the majority of perfusion-CMR guided pathways.

CMR IN PATIENTS WITH CHEST PAIN BUT NO SIGNIFICANT CORONARY ARTERY DISEASE

CMR is highly valuable tool in the assessment of the underlying etiology of a multitude of cardiovascular diseases due to its ability to assess function, regional or diffuse fibrosis, edema due to inflammatory processes and micro-vascular flow. For this reason, CMR is the main diagnostic modality used after a negative coronary angiography in patients who present with chest pain and a positive troponin test [13]. In patients with this syndrome– originally known as myocardial infarction with normal coronary arteries (MINOCA), CMR was reported as being able to elucidate in 87% of cases the underlying mechanism of the troponin rise [14], with the most frequent causes being myocarditis, takotsubo cardiomyopathy or acute myocardial infarction. Furthermore, other causes of chest pain in patients with low pre-test likelihood for CAD, such as pericarditis, myocarditis or micro-vascular disease can be identified by CMR; these would be missed if invasive or computed tomography coronary angiography were used to rule out coronary disease.

GUIDELINE RECOMMENDATIONS

Perfusion-CMR is cited in all international guidelines for the detection of coronary artery disease. In the ESC and EACTS guidelines for revascularization (2018) and stable coronary artery disease (2013), perfusion-CMR was given a Class Ia recommendation for symptomatic patients with intermediate pre-test probability for CAD. In addition, the 2013 ESC guidelines on the management of stable coronary artery disease recommend, for the above class of patients, an imaging stress test, including perfusion-CMR, instead of stress ECG, if the appropriate local expertise is available. Furthermore, perfusion–CMR is one of the imaging stress tests that should replace stress ECG in those patients
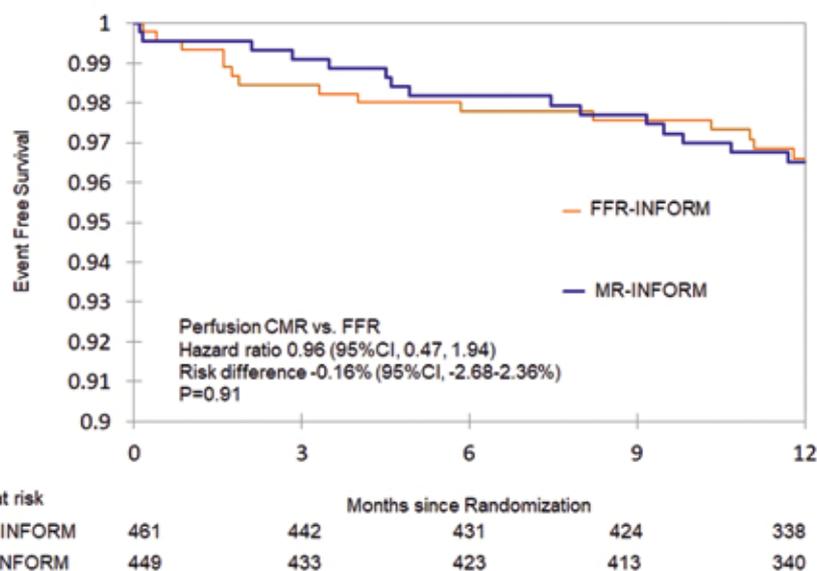
The recently published MR-INFORM trial [9] is an international, randomized controlled trial, which compared the clinical effectiveness of a perfusion-CMR guided strategy with an FFR-guided strategy to manage patients with chest pain and medium to high pre-test probability of CAD. The results indicate that perfusion-CMR can guide further management as effectively as invasive angiography supported by FFR [Figure 1]. In the study, 918 patients with stable chest pain, ≥2 risk factors or positive ECG stress test were randomized into a non-invasive arm guided by stress perfusion-CMR or an invasive arm guided by angiography with supplementary FFR. All patients received guideline-directed medical therapy. In the CMR-informed arm only 40.5% required an invasive angiography despite an intermediate to high pre-test likelihood of 74% according to a modified Diamond and Forrester score and fewer patients were revascularised

"... The results indicate that perfusion-CMR can guide further management as effectively as invasive angiography supported by FFR..."

Figure 2. Kaplan-Meier curves of event free survival of the MR-INFORM trial. The blue curve denotes the patients guided by perfusion-CMR. The orange curve denotes the patients guided by invasive angiography and fractional flow reserve. Image copyright: Eike Nagel, on behalf of the MR-INFORM investigators.

who have ECG abnormalities that make the interpretation of ECG during stress difficult. According to the same guidelines, symptomatic patients with prior revascularization either by coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI) benefit from an imaging stress test such as perfusion-CMR [15,16]. ACC appropriateness criteria from 2014 consider perfusion-CMR as appropriate in patients with intermediate pre-test probability and non-diagnostic exercise ECG as well as in patients with high pre-test probability independently of the interpretability of the exercise ECG [17]. These guidelines are currently being updated.

SUMMARY

As demonstrated by the evidence presented in this article, perfusion-CMR is a powerful diagnostic tool for the work-up of patients with stable chest pain. New evidence may further expand the use of perfusion-CMR in clinical practice into a broader spectrum of patients, particularly those with low- to intermediate- pre-test probability, where a negative test carries a favorable prognosis and also frequently allows the identification of the underlying non-coronary cause of the symptoms. More importantly

though, in patients with intermediate to high pre-test likelihood for CAD, the current invasive strategy can be safely replaced by a 30-minute imaging test, thus obviating the need for radiation exposure or invasive access.

REFERENCES
1. Jaarsma C, Leiner T, Bekkers SC, Crijns HJ, Wildberger JE, Nagel E, et al.. Diagnostic Performance of Noninvasive Myocardial Perfusion Imaging Using Single-Photon Emission Computed Tomography, Cardiac Magnetic Resonance, and Positron Emission Tomography Imaging for the Detection of Obstructive Coronary Artery Disease. Journal of the American College of Cardiology. 2012 May; 59(19): 1719–28.
2. Kiaos A, Tziatzios I, Hadjimiltiades S, Karvounis C, Karamitsos TD. Diagnostic performance of stress perfusion cardiac magnetic resonance for the detection of coronary artery disease: A systematic review and meta-analysis. Int J Cardiol. 2018 Feb 1; 252: 229–33.
3. Takx RAP, Blomberg BA, Aidi El H, Habets J, de Jong PA, Nagel E et al. Diagnostic accuracy of stress myocardial perfusion imaging compared to invasive coronary angiography with fractional flow reserve meta-analysis. Circ Cardiovasc Imaging. 2015 Jan; 8(1): e002666–6.
4. Schwitter J, Wacker CM, van Rossum AC, Lombardi M, Al-Saadi N, Ahlstrom H, et al. MR-IMPACT: comparison of perfusion-cardiac magnetic resonance with single-photon emission computed tomography for the detection of coronary artery disease in a multicentre, multivendor, randomized trial. European Heart Journal. 2008 Jan 3; 29(4): 480–9.
5. Greenwood JP, Maredia N, Younger JF, Lancet JBT, 2012. Cardiovascular magnetic resonance and single-photon emission computed tomography for diagnosis of coronary heart disease (CE-MARC): a prospective trial. Lancet. 2012 Feb 4; 379(9814): 453-60.
6. Lipinski MJ, McVey CM, Berger JS, Kramer CM, Salerno M. Prognostic value of stress cardiac magnetic resonance imaging in patients with known or suspected coronary artery disease: a systematic review and meta-analysis. J Am Coll Cardiol. 2013 Aug 27; 62(9): 826–38.
7. Shaw LJ, Berman DS, Picard MH, Friedrich MG, Kwong RY, Stone GW, et al. Comparative definitions for moderate-severe ischemia in stress nuclear, echocardiography, and magnetic resonance imaging. JACC: Cardiovascular Imaging. 2014 Jun; 7(6): 593–604.
8. Puntmann VO, Carr-White G, Jabbour A, Yu CY, Gebker R, Kelle S, Rolf A, Zitzmann S, Peker E, D'Angelo T, Pathan F, Elen, Valbuena S, Hinojar R, Arendt C, Narula J, Herrmann E, Zeiher AM, Nagel E; International T1 Multicentre CMR Outcome Study. Native T1 and ECV of Noninfarcted Myocardium and Outcome in Patients With Coronary Artery Disease. J Am Coll Cardiol. 2018 Feb 20;7 1(7): 766-778
9. Nagel E, Greenwood JP, McCann GP, Bettencourt N, Shah AM, Hussain ST, et al. Magnetic Resonance Perfusion or Fractional Flow Reserve in Coronary Disease. N Engl J Med. 2019 Jun 20; 380(25): 2418–28.
10. Walker S, Girardin F, McKenna C, Ball SG, Nixon J, Plein S,et al. Cost-effectiveness of cardiovascular magnetic resonance in the diagnosis of coronary heart disease: an economic evaluation using data from the CE-MARC study. Heart. 3rd ed. 2013 Jun; 99(12): 873–81.
11. Moschetti K, Petersen SE, Pilz G, Kwong RY, Wasserfallen J-B, Lombardi M, et al. Cost-minimization analysis of three decision strategies for cardiac revascularization: results of the "suspected CAD" cohort of the european cardiovascular magnetic resonance registry. J Cardiovasc Magn Reson. 2016 Jan 11; 18: 3.
12. Pontone G, Andreini D, Guaricci AI, Rota C, Guglielmo M, Mushtaq S, et al. The STRATEGY Study (Stress Cardiac Magnetic Resonance Versus Computed Tomography Coronary Angiography for the Management of Symptomatic Revascularized Patients): Resources and Outcomes Impact. Circulation: Cardiovascular Imaging. Lippincott Williams & Wilkins Hagerstown, MD; 2016 Oct; 9(10). pii: e005171
13. Ibáñez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). European Heart Journal. 2017 Aug 26; 39(2): 119–77.
14. Pathik B, Raman B, Mohd Amin NH, Mahadavan D, Rajendran S, McGavigan AD, et al. Troponin-positive chest pain with unobstructed coronary arteries: incremental diagnostic value of cardiovascular magnetic resonance imaging. European Heart Journal - Cardiovascular Imaging. 2016 Oct; 17(10): 1146–52.
15. Neumann F-J, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. European Heart Journal. 2019 Jan 7; 40(2): 87–165.
16. 2013 ESC guidelines on the management of stable coronary artery disease. Eur Heart J. 2013 Oct 7; 34(38): 2949–3003.
17. Wolk MJ, Bailey SR, Doherty JU, Douglas PS, Hendel RC, Kramer CM, et al. ACCF/AHA/ASE/ASNC/HFSA/HRS/SCAI/SCCT/SCMR/STS 2013 Multimodality Appropriate Use Criteria for the Detection and Risk Assessment of Stable Ischemic Heart Disease. Journal of the American College of Cardiology. 2014 Feb;63(4):380–406.